Dysregulated Gene Expression During Hematopoietic Differentiation From Human Embryonic Stem Cells.

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Public Summary:
It is well recognized from adult stem cell studies that the growth of transplanted bone marrow or cord blood is generated from the hematopoietic ("blood-forming") stem and progenitor cells provided by the donor. Mature, differentiated cells that accompany the hematopoietic stem cells, disappear rapidly after transplantation as they lack the ability to self-renew. It is thus essential when designing clinical approaches that use tissue derived from human embryonic stem cells (hESC), to specifically target the production of stem and progenitors that will survive, proliferate and differentiate normally after transplantation. In this report we show that the types of progenitors that hESC produce under current conditions are more limited functionally than those found in cord blood. Through a comprehensive analysis we identified some of the key genetic differences in the way blood is formed from hESC that may be particularly important in the formation of the lymphoid cells of the immune system.

Scientific Abstract:
The generation of hematopoietic cells from human embryonic stem cells (hESC) has raised the possibility of using hESC as an alternative donor source for transplantation. However, functional defects identified in hESC-derived cells limit their use for full lymphohematopoietic reconstitution. The purpose of the present study was to define and quantitate key functional and molecular differences between CD34(+) hematopoietic progenitor subsets derived from hESC and CD34(+) subsets from umbilical cord blood (UCB) representing definitive hematopoiesis. Two distinct sub-populations were generated following mesodermal differentiation from hESC, a CD34(bright) (hematoendothelial) and CD34(dim) (hematopoietic-restricted) subset. Limiting dilution analysis revealed profound defects in clonal proliferation relative to UCB particularly in B lymphoid conditions. Transcription factors normally expressed at specific commitment stages during B lymphoid development from UCB-CD34(+) cells were aberrantly expressed in hESC-derived CD34(+) cells. Moreover, strong negative regulators of lymphopoiesis such as the adaptor protein LNK and CCAAT/enhancer-binding protein-alpha (CEBPalpha), were exclusively expressed in hESC-CD34(+) subsets. Knockdown of LNK lead to an increase in hematopoietic progenitors generated from hESCs. The aberrant molecular profile seen in hESC-CD34(+) cells represents persistence of transcripts first expressed in undifferentiated hESC and/or CD326-CD56(+) mesoderm progenitors, and may contribute to the block in definitive hematopoiesis from hESC.